

IS EPILEPSY A DISEASE OF METABOLISM? A REVIEW OF THE LITERATURE.*

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It has been and is the hope of all that by an exact study of the vital processes of epileptics during life and of their tissues after death, some light might be thrown on the nature of the disease. Patient and accurate pathological work has yielded no changes which can be found in cases of every form and duration, and many believe that the primary nature of the changes which have been reported is open to doubt. The cause of the disease, if there be one in an organic sense, is still to be discovered. I do not wish to be understood as denying the possibility of an organic lesion. There must be such a lesion. I do, however, most seriously doubt, whether this lesion is one which can be made visible by the methods of the pathologist. I believe that the epileptogenous change affects the chemical structure of the cell—whether this change is visible or invisible, seems to me immaterial.

The common idea of the cell is a morphological one. I wish, however, to direct your attention to a chemical conception of the cell and its activities. I believe with Vaughn (under whom I had the privilege of working) that "the cell is a chemical compound of very complex, but of definite structure." This theory differs from others in the emphasis placed on the definite chemical nature of the cells. Thus function is the result of change in the chemical structure of the cell, brought about in accordance with the laws governing chemical action. Disease being a change or failure of normal function, it follows that disease is the result of interference with the normal chemical processes of the cell, either from inherent tendencies or by the action of external agents.

Such a conception of the cell and of disease, authorizes the application of chemical methods to problems which have hitherto been the exclusive province of the pathological anatomist.

Even could we point out a visible lesion in epilepsy we

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should be but little nearer an understanding of the disease. We should still have to ask how this particular lesion produced the disease, and, more important yet, we should have to seek the cause of the lesion. If the activities of the cell are carried out as I have indicated, by chemical means, bio-chemical methods can be logically applied, and offer, from their searching and accurate nature, great hope of light in what is now darkness.

The absence of a visible lesion led to the assumption that endogenous poisons or metabolic disturbances were the cause of the disease. Clinical analogies to other autointoxications have led some to accept this view, but such analogies, while presenting contributory evidence, are not direct proof,—a poison or a disturbance in metabolism must be demonstrated experimentally.

The urine being the most easily obtained of the fluids of the body, has received the most attention. While the old idea that the attack was always followed by the voiding of urine has been found wrong, it is generally stated that the epileptic is given to polyuria, especially following the attack. Krainsky reports daily amounts of two to three liters, and states that four are not unusual. Rabow, and Voisin and Petit report an increased volume after the attack. Féré speaks of crises of polyuria. Bleile and Ferrannini find no change, and Alessi and Pierri report the urine scanty. An increased specific gravity is reported, especially after the attacks, and this, with the increased volume, would seem to indicate an increase of excretory products at the time of the attacks.

Albumin in the post-paroxysmal urine was first noted by Seyfert, in 1854. Others, Rabow, Furstner, Otto, Fiori, Hallager, and Kleudgen, report its presence as rare and inconstant, and in this opinion Binswanger agrees. Voisin, however, finds it in about half the cases and other authors are in practical agreement with him. Huppert and Dewitt find that the amount of albumin depends on the time elapsed after the seizure and on the severity of the seizure. Brunninghausen finds it in the greater number of cases, but of irregular occurrence in the same case. Galenti found 0.05 to 2.0 per cent. Lanois and Mairet found it 29 times out of 50, and Klein 14 times of 23.

Albumin in the post-paroxysmal urine would appear to be of more than rare appearance. We must consider, however, the possibility of concurrent renal disease and of errors in the recognition of albumin. The fact that it is found only in the early hours after the attack, may explain some of the negative findings. The whole ground must be gone over again, using methods of unquestioned accuracy and studying a large number of cases.

Sugar has been found in epileptic urine, but the general opinion seems to be that its occurrence is not an epileptic phenomenon.

Of the inorganic constituents of the urine, the chlorides and the phosphates have been most studied. Vires finds the former increased, while Mairret and Bosc report them decreased and Agostini does not find them increased. Krainsky finds no relation of chlorine to the attack.

The phosphorus metabolism has been more extensively studied. Gibson, Ecchevera and Mendel, Voisin, Mairret, Krainsky, Agostini, Lepin, Egremont, Aubert, and Mairret and Bosc find phosphoric acid increased after the seizure. Lepin and Jaquin, and Mairret and Vires find an increase of the earthy phosphates relative to the alkaline, which may even be decreased. Féré and Herbert cannot substantiate this. Adenine and Bonelli find the earthy phosphates decreased in both urine and feces and report excellent results from the administration of calcium. Mairret associates the earthy phosphates with brain activity. Lepin, Egremont, and Aubert find an increase of organic phosphorus. This is also reported in degenerative nervous diseases by Symers. If this can be confirmed, and the phosphorus shown to be present as compounds other than neucleo-albumins, we shall have an important fact, for organic phosphorus is an important constituent of nerve tissue.

Agostini, Dide and Strenuit, Nelson Peter, Vires, Voisin, Mairret and Bosc, and Rabow report an increase of urea. Teeter finds it variable. Krainsky and Bleile find no constant relation to, and Alessi and Pierri, and Rabow find a decrease after, the attack. We must take into consideration the imperfect methods for the estimation of urea generally used. That the

majority agree on an increase is to some extent a check on the accuracy of their work.

Haig brings forward uric acid as the cause of the attack, having found a retention before and an increased excretion after the attack. Caro, Guidi, and Krainsky confirm his results. The latter does not believe that uric acid is the actual poison but that some antecedent substance, readily transformed into uric acid, by changes in the body fluids, is responsible. Bleile, Herter and Smith, Putnam and Pfaff, and Mainzer do not get results favorable to Krainsky's view. Paraxanthin was found in relation to some epilepsies by Rachford.

Galenti and Savini find the etherial sulphates increased and Galenti and Herter and Smith find indican increased. These results are in cases with indigestion.

Acetone has been found by Hoppe in 8.5 per cent. of 325 cases, but never after single attacks. Rivano found it after attacks in 30 per cent. of his cases. Hoppe observes that acetone is generally found in cases where the taking of food was interfered with; this probably accounts for its occurrence.

Benedicenti and Galdi and Tarugi find an increase of urinary acidity.

The toxicity of the urine has been much studied to determine if there was a retention or an increased excretion of poisonous matters in relation to the attack. Normal urine has a certain degree of toxicity. Deny and Choupe, Ferrannini, Voison and Peron, Tramonti and Obriga find the interval and ante-paroxysmal urine less toxic than normal urine or the urine from after the attack. Mariet and Bosc, Féré, Agostini, Galdi and Tarugi find the post-paroxysmal urine less toxic than that of other times. All except Hebold and Bratz find an increase in toxicity in relation to the time of the attack, but differ as to the exact time of maximum and minimum toxicity. The method is probably responsible for this difference of opinion. The saline concentration and the reaction of the urine, the rate of injection and the susceptibility of the experimental animal into which the intravenous injection is made are all variable factors. The method is at best a crude one.

The cause of the toxicity of normal and epileptic urines appears to be the same, the symptoms from both being alike. Osmotic action, the toxic potassium ions, the coloring

matters, uric acid perhaps, and, according to some, alkaloidal bodies, all play an important part. The toxicity is not due to one substance, but is the sum of all.

Cabitto found the sweat of epileptics more toxic just before the attacks; the toxicity afterward and during the interval is normal. Mairet and Ardin-Delteil find the highest toxicity during or after the attack. Mavrojannis finds no change. The method used is the same as that used with urine.

Belisari, Agostini, and Leubuscher report the hydrochloric acid of the gastric juice increased by the attack. Agostini finds the toxicity of the gastric juice increased just before the attack, corresponding to the transitory dyspepsia.

As regards the cellular composition of the blood no changes have been established as peculiar to the epileptic. Claus and Van Der Stricht report the density of the blood lowered, and Lui, Charon and Briche, and Pugh find the alkalinity diminished before the attack, to rise afterward.

Chiaruttini and Cololian found the toxicity of the blood greater at the time of the attack. Mairet and Vires found the blood hypotoxic in the interval. Herter found no special toxicity. Krainsky, injecting blood taken just before an attack, produced both immediate and repeated seizures in a rabbit, and Pearce and Boston performing a similar experiment on a case of pernicious anemia, got a similar result. Geni finds the blood of epileptics more teratogenic than normal blood. He also reports that the blood during the exacerbations of the disease is much more toxic than during the intervals.

Geni's work on the serum treatment of epilepsy, if it can be confirmed, will give us absolute evidence of a toxin for the disease. But before it can be accepted, it must be verified under the most rigorous conditions, with careful controls of the hygiene and medication employed. Longer periods of observation and larger series of cases must be employed, and the theoretical side carefully studied.

Comberali and Bue and Voisin have reported staphylococci in epileptic blood. Brä found the "neurococcus" in the blood of a large proportion of the epileptics he examined, but could find it only at the time of the attacks. This fact he uses to explain previous failures. Besta, Tirelli and Bossa cannot duplicate his work, and it is quite possible that he was dealing

with a skin contamination. It is interesting to note, however, that Tirelli reports increased bacteriocidal power of epileptic blood against staphylococci.

Mott and Halliburton and Donath have found cholin in the cerebro-spinal fluid of degenerative nervous diseases and of epilepsy, and Donath believes it to be the cause of the convulsion. The presence of cholin has been doubted by several authors, and, again, others have confirmed its finding. The question centers around the accuracy of the separation and identification of cholin, those who doubt its presence claiming that the product obtained is an ammonia or potassium compound and not cholin. Its presence could be easily understood as it is a product of the cleavage of myelin, and it has been shown that after death there is an enzyme which can bring about this cleavage. One can imagine that under favorable conditions this enzyme could become active during life. Injected into the circulation, cholin is not convulsive, but according to Donath, its direct application to the brain does produce convulsions. The mechanical effect is to be taken into consideration, however. Even though cholin is not ordinarily a convulsive poison, it is to be remembered that the epileptic brain is inherently sensitive, and it responds actively to irritants which would have no action on the normally constituted brain.

While this review of the literature is an exceedingly meager one, it will be seen that there are changes in the metabolism of the epileptic and in the toxicity of his body fluids. Just what these changes are and their time of occurrence is doubtful because of contradictory findings. The fact that some variation from the normal is almost always reported, makes one hopeful that further work along bio-chemical lines, conducted with the greatest care, using the most exact methods, carefully controlling every possible factor, and using a goodly number of cases, will in the end bring a solution of the problem.

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